PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference CHME-PWO-002	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2004/036143	International filing date *(day/month/year)* 29 October 2004 (29.10.2004)	Priority date *(day/month/year)* 31 October 2003 (31.10.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant CHILDREN'S MEDICAL CENTER CORPORATION		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 01 May 2006 (01.05.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Authorized officer Nora Lindner Telephone No. +41 22 338 89 65

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

PCT

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/US2004/036143	International filing date *(day/month/year)* 29.10.2004
Priority date *(day/month/year)* 31.10.2003	
International Patent Classification (IPC) or both national classification and IPC C12N5/08, C12N5/06, G01N33/53	
Applicant CHILDREN'S MEDICAL CENTER CORPORATION	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Vollbach, S

Telephone No. +49 89 2399-8715

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/036143

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4,6-11
	No:	Claims	5,12,13
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-13
Industrial applicability (IA)	Yes:	Claims	1-13
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

D1: MCNAGNY K M ET AL: "Thrombomucin, a novel cell surface protein that defines thrombocytes and multipotent hematopoietic progenitors" THE JOURNAL OF CELL BIOLOGY, ROCKEFELLER UNIVERSITY PRESS, US, vol. 138, no. 6, 1997, pages 1395-1407, XP002232095 ISSN: 0021-9525

D2: WO 03/068937

D3: GU JIAN-MING ET AL: "Disruption of the endothelial cell protein C receptor gene in mice causes placental thrombosis and early embryonic lethality." 8 November 2002 (2002-11-08), JOURNAL OF BIOLOGICAL CHEMISTRY, VOL. 277, NR. 45, PAGE(S) 43335-43343 , XP008042848 ISSN: 0021-9258

D4: CRAWLEY JAMES T B ET AL: "Distribution of endothelial cell protein C/activated protein C receptor (EPCR) during mouse embryo development" THROMBOSIS AND HAEMOSTASIS, vol. 88, no. 2, August 2002 (2002-08), pages 259-266, XP002317742 ISSN: 0340-6245

Re Item V:

The present application relates in independent form to methods for obtaining a population of hematopoietic stem cells (claim 1) and EPCR+ cells (claim 6), the haematopoietic stem cells and the EPCR+ cells and their medical use in transplantation processes.

Methods for obtaining populations of cells with a particular cell surface marker are widely known in the art (see D1 and D2). D1 e.g. discloses a method for the purification of hematopoietic stem cells using thrombomucin as a cell surface marker.
The endothelial cell protein C receptor has extensively been studied and its expression could be detected already in the early development on trophoblast giant cells of the trophectoderm (see D3) and in trophoblasts of the placenta. In the embryo expression can be detected on endothelial cells of e.g larger blood vessels (D4).

Given the information of D1 or D2 i.e. methods for obtaining cells, in combination either with D3 or D4 which indicate on which cell types the EPCR is expressed, the method for the purification of obtaining EPCR+ cells according to claims 6-11 cannot be regarded to involve an inventive step as required by Article 33(3) PCT.
As far the more specific method according to claims 1- 4 for the purification of hematopoietic stem cells is concerned, the present authority considers the presence of the EPCR on haematopoietic stem cells obvious, because of its importance in the embryonic development and its presence on progenitors such as trophoblast cells.
In addition, the claims directed to the cell population according to claims 5 and 12 are not new with respect to the cells disclosed in D1. The reason is that the surface marker by which the cells have been selected are inherently present on cell population selected with the help of a distinct surface marker. Therefore these claims lack novelty as set out in Article 33(2) EPC. The same applies to method claim 13 which lacks novelty with regard to D2.

Re Item VIII.

Independent methods according to claim 1 and claim 6 are identical in their process steps. However in the first method hematopoietic stem cells are selected whereas in the second method all cells expressing the EPCR+ marker are identified. There are two possibilities:
Either all EPCR+ cells are haematopoietic stem cells. In this case drafting of two independent method claims is superfluous, because of its identical scope of protection
or
haematopoietic stem cells are a subpopulation of EPCR+ cells. In that case an essential technical feature is lacking in the method of claim 1 (Article 6 PCT).